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Some Approaches to the Study of the Clinical Implications of Thyroid Alterations in Post-Traumatic Stress Disorder

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BACKGROUND: HORMONAL STUDIES IN PTSD

Post-traumatic Stress Disorder (PTSD) in male Vietnam combat veterans has been found to be associated with multiple hormonal alterations involving the cortisol, norepinephrine, epinephrine, testosterone, and thyroid systems (1–8). Early psychoendocrine studies revealed preliminary evidence of an unusual hormonal profile in PTSD, with the overall balance shifted towards low cortisol levels (1,2), high norepinephrine and epinephrine levels (3,4), a high norepinephrine/cortisol ratio (5), high testosterone levels (6), and high total thyroxine (T4) levels in the face of lower free T4 levels (7).

We have recently reported a follow-up study involving a much larger sample of PTSD patients and a broader profile of thyroid assays that has uncovered the striking new finding that many PTSD patients show persistent and disproportionate elevations in both total and free triiodothyronine (T3) in relation to free thyroxine (T4); this elevates the T3/T4 ratio, suggesting that there may be increased peripheral conversion of T4 and T3 in this disorder (8). The study sample included 96 male Vietnam combat veterans with PTSD (4 subsamples of 24 patients each) and 24 male control subjects.

Figure 1 presents a summary of the main thyroid findings, with the PTSD patients showing highly significant elevations in total T3, free T3, and total T4 in the presence of no significant change in free T4, so that the total T3/free-T4 ratio is consequently elevated. It should be noted that the graph presents standardized scores around an arbitrary mean of 10 for each hormone, so that the height of the bars does not indicate absolute hormonal levels but rather the *relative* levels of the patient group versus the control group, showing the marked elevations in the PTSD group in all measures except the free T4 levels. Although a detailed interpretation of this profile is complicated somewhat by the additional presence of a concurrent serum thyroxine-binding globulin (TBG) elevation in the PTSD patients, as reported elsewhere (8), the presence of a marked elevation in *free* T3 levels

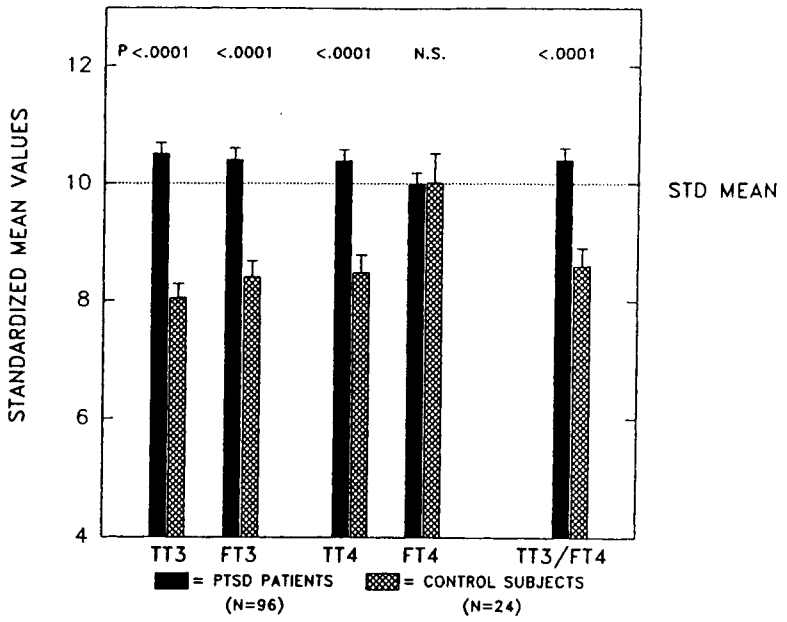

FIG. 1. Summary of thyroid hormone alterations in PTSD.

and in the T3/T4 ratio lends strong support for the hypothesis that the overall profile reflects not only TBG elevation but also increased production of T3 from T4.

As shown in Fig. 2, which is a simplified diagram of the hormonal production pathways of the hypothalamic-pituitary-thyroid axis, the centrally initiated influence of the hypothalamic thyrotropin-releasing hormone (TRH), acting through the anterior pituitary thyroid-stimulating hormone (TSH), is primarily involved in stimulating the secretion of T4 and probably only accounts for about 20% or less of the total T3 production in the body. It is important to realize that by far the greatest source of T3 production, probably at least 80%, is from peripheral enzymatic monodeiodination of T4 in extrathyroidal tissues such as liver and muscle (9,10). It is also noteworthy that one of the factors that appears to promote increased T3 conversion from T4 is elevation of peripheral catecholamine levels (11,12), a condition known to be prominent among the sustained hormonal alterations in PTSD (3,4).

In viewing the PTSD thyroid profile summarized in Fig. 1, then, the pattern of elevated T3 levels in the face of relatively lower free T4 levels might well be explained if the latter hormone were being "used up" excessively to produce increased amounts of T3. As detailed elsewhere, total T4 elevation probably is secondary mainly to an increase in TBG levels and possibly some central stimulation, although TSH levels are not significantly elevated in PTSD patients (8). A sense of the considerable extent to which PTSD patients tend towards elevation of the total T3/free-T4 ratio can be gained from Fig. 3, which presents all the raw data from the individual control subjects and patients, showing that 85% of the patients have values above the mean level for the control group. The first sample of 24 patients (PTSD-1) was from the Menlo Park VA Medical Center and the remaining three samples were from the West Haven VA Medical Center.

It should also be pointed out that our group of control subjects was composed mostly of veterans, some of whom had combat experience,

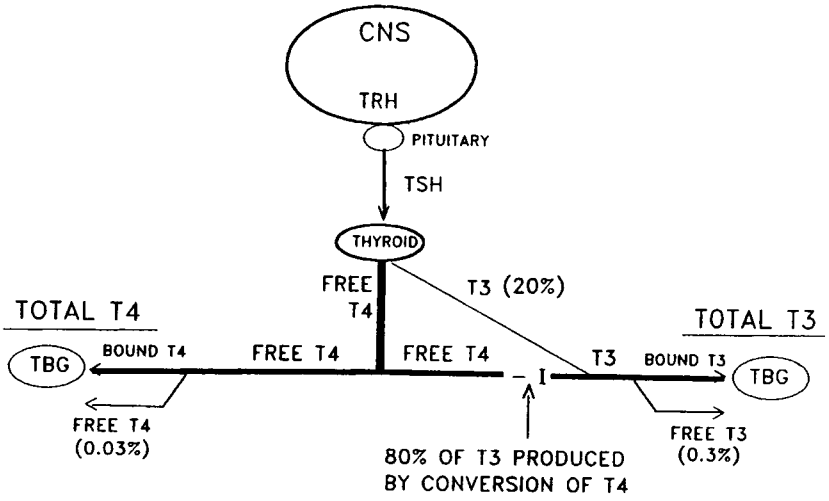

FIG. 2. Organization of the hypothalamic-pituitary-thyroid system.

with Mississippi PTSD Scale scores ranging up to 81 that raise the possibility that they may represent a subsample with partial or mild PTSD. Figure 4 shows that this subsample with combat exposure has a mean total T3 level intermediate between the patients meeting DSM-III-R criteria for PTSD and the control subjects without combat experience. The full extent of the difference between PTSD patients and normal control subjects without exposure to combat,

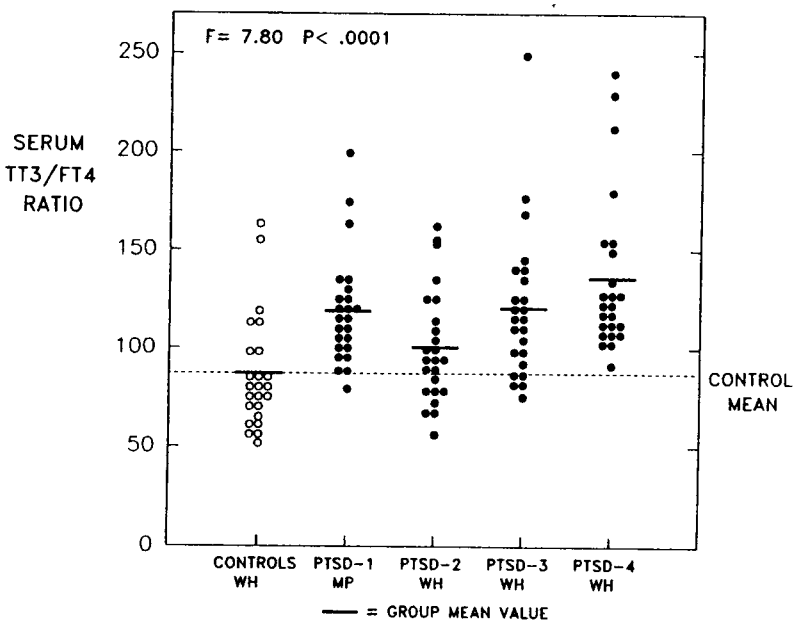

FIG. 3. TT3/FT4 ratio elevations in multiple samples of PTSD patients.

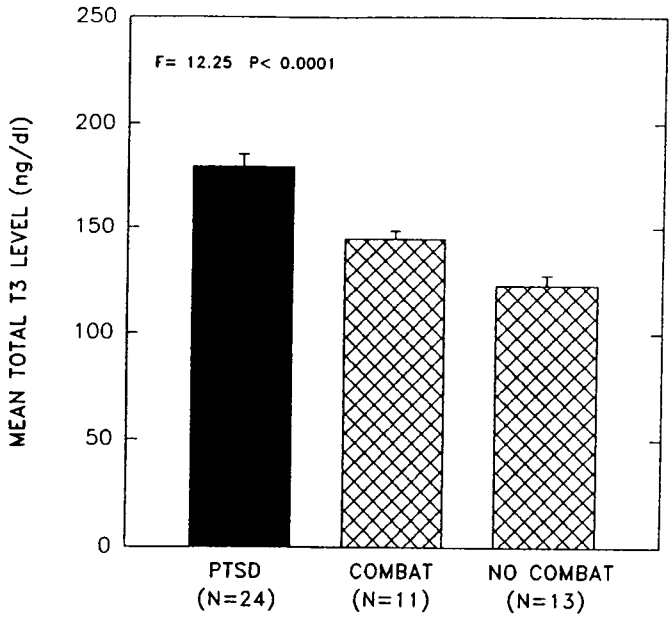

FIG. 4. Total T3 levels in PTSD versus combat and noncombat controls.

therefore, may be somewhat underestimated in our study.

SOME HISTORICAL CONSIDERATIONS

It has long been known that a history of traumatic stress, especially life-threatening crises such as combat experiences, fires, earthquakes, shipwrecks, narrow escapes from accidents, etc., is a common antecedent to the onset of thyrotoxicosis (13,14). Many preclinical studies in both normal humans and animals have shown alterations in thyroid hormone secretion in response to psychologically stressful situations (15). Many clinical studies have provided evidence that thyroid hormones may have a significant role in a variety of psychiatric illnesses, including both affective and schizophrenic disorders (16,17,18). With such strong support for considering the thyroid hormones as "stress hormones," it should perhaps not be surprising to find thyroid alterations in PTSD, by definition a stress-related disorder.

Yet the nature of the observed changes in PTSD are not those of classical or other established forms of clinical hyperthyroidism, but rather of a more subtle, unusual, and perhaps even distinctive type of moderate hyperactivity featuring total and free T3 elevations that are not detected by conventional routine clinical thyroid screening tests and have therefore been overlooked until very recently. The fact that T3 is metabolically two to four times more potent than T4, along with the observation that 64% of our large sample of PTSD patients had total T3 levels above the upper range limit of the control subjects (8), clearly stimulate interest in exploring the possibility that T3 elevations may have a significant clinical role in PTSD, either in reflecting or contributing to pathogenetic factors.

It is, of course, well known that the clinical picture of classical hyperthyroidism includes such psychiatric symptoms as sleep disturbances, restlessness, anxiety, irritability, explosive anger, jumpiness or increased startle, and difficulty in concentrating—in other words, both cognitive and affective disturbances commonly observed in PTSD patients (19). It should also be kept in mind that many previous psychoendocrine studies, particularly those of the cortisol system, have clearly demonstrated that both state

or phase factors, such as emotional arousal, as well as trait or characterological factors, such as coping or defensive styles, are reflected in hormonal levels (20). In beginning to pursue an understanding of the clinical significance of the thyroid alterations in PTSD, then, it appears well advised to consider and search for both enduring and transitory clinical or psychological correlates of the elevated T3 levels in PTSD, using both cross-sectional and longitudinal approaches. As the present study unfolded and we became increasingly aware of the unusual thyroid findings, we began in an exploratory way to utilize our core battery of PTSD assessment scales, along with the psychometric measurements available from other concurrent clinical studies involving our patient sample and, as possible, finally began to add psychometric measurements that would permit some screening for personality or trait factors as well as state and symptom factors. The purpose of this chapter is to review some of these preliminary efforts to look for relationships between clinical or psychological factors and the T3 elevations in PTSD, and to consider some important methodological and research strategy issues emerging in our experience so far that appear likely to have important implications for future work in this field.

LONGITUDINAL COURSE OF T3 LEVELS IN PTSD INPATIENTS

In the West Haven PTSD inpatient sample, we were able to obtain hormonal samples at three points during hospitalization—at admission, midcourse, and discharge—on a subsample of 47 patients. Figure 5 shows that the mean total T3 level for this PTSD patient group is similar at the admission and middle points, but drops significantly at the discharge point (ANOVA for repeated measures, $F=7.77$, $p<0.0008$), so that it clearly appears likely that T3 levels may covary with changes in clinical state or phase of illness on a longitudinal basis. It is also of interest, however, that at all three points the PTSD patients sustain T3 levels significantly above the control mean value ($F=53.62$, $p<0.0001$), which appears to support the possibility that there are also important relationships

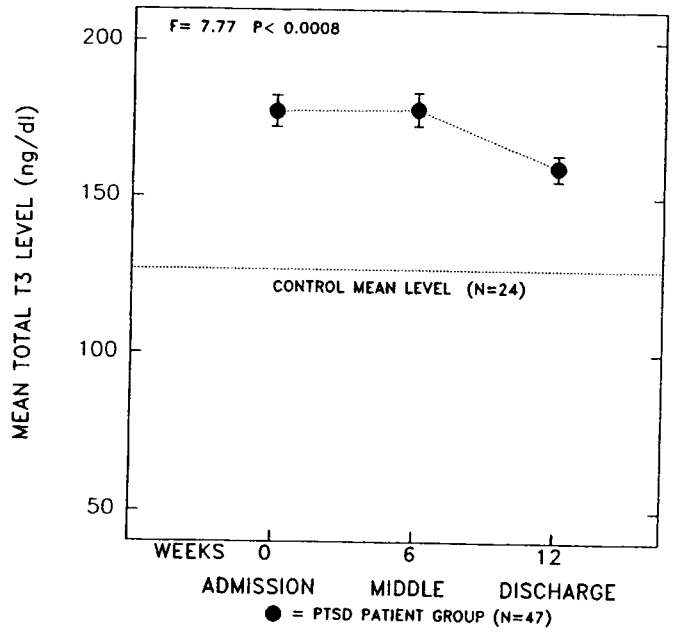

FIG. 5. Longitudinal course of total T3 levels in PTSD inpatients.

between T3 levels and relatively enduring psychological traits or clinical characteristics in PTSD patients.

As a further way of examining state or phase fluctuations over time, the changes in T3 levels in individual patients between the period of hospital admission and the period of hospital discharge were analyzed in our West Haven sample of patients. These patients were admitted in 6 successive cohorts, ranging from 8 to 13 men each, for a 12-week inpatient treatment program involving an intensive schedule of about 32 hours a week of individual and group therapy. The change or difference in total T3 levels between the admission and discharge periods was calculated as a "delta" value, and Fig. 6 presents all the raw data for individuals within the six cohorts. Notice that about 70% of the patients show changes greater than 20 ng%, either increases or decreases, between these two points in time. There are clearly great individual differences between subjects, with the range extending from +74 to −105 ng%. While about 30% of the patients show increases and 70% show decreases, there appears to be some interesting variation between the group mean values, indicating not only an individual but also a cohort or group tendency towards either an increase or a decrease over the course of hospitalization.

An anecdotal example of longitudinal T3 changes in a single cohort of PTSD patients is presented in Fig. 7, showing an apparent relationship of hormonal changes to the phase of treatment. The marked elevation in total T3 levels in six out of seven patients during the middle phase of the treatment program appeared coincident with the initiation of traumatic memory sessions, in which each man recounted in a group setting the most distressing memory of his combat experience. The degree, however, to which patients earnestly participated in these disturbing sessions appeared to vary considerably from cohort to cohort, as well as from individual to individual, and was often difficult to assess, so that the situational criterion of a traumatic memory session alone was not a sufficient basis for developing a "challenge" model for psychoendocrine studies.

The findings presented in both Figs. 6 and 7, demonstrating such examples as the same patient having a total T3 value of 245 ng% at one point

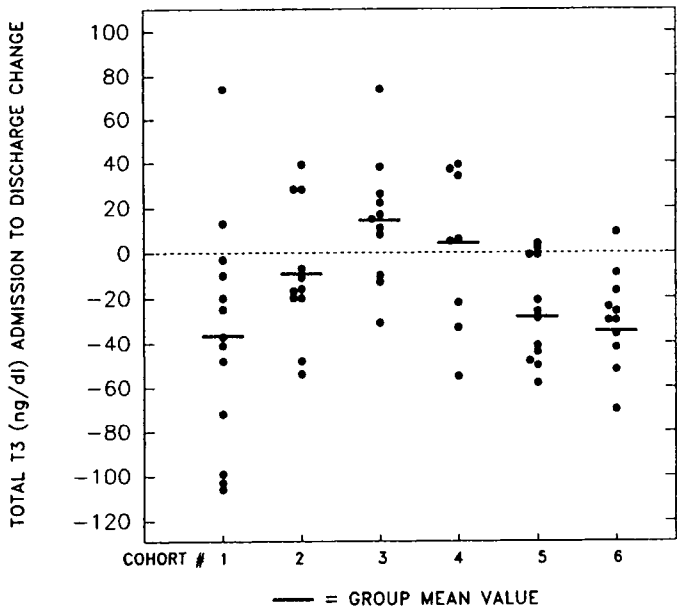

FIG. 6. Admission to discharge change in total T3 levels in PTSD cohorts.

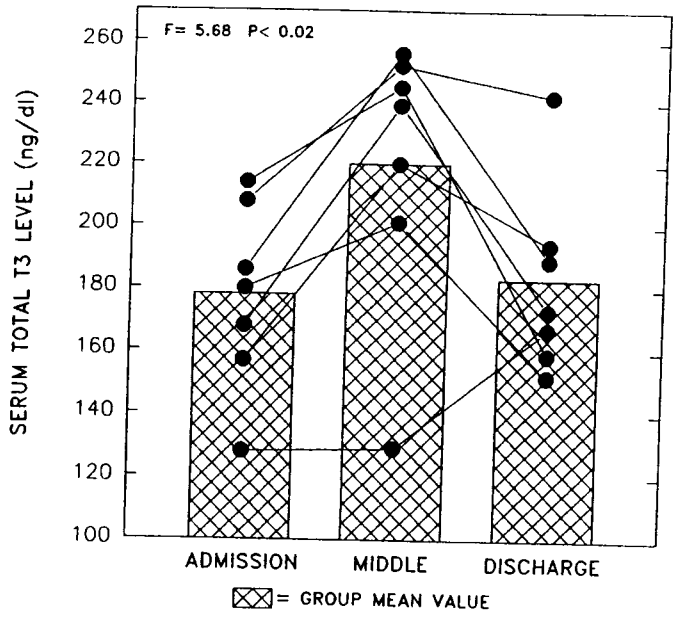

FIG. 7. Total T3 change in relation to treatment phase in PTSD cohort.

in time and 160 ng% at another point, raise the question as to whether such T3 changes might be related simply to concurrent changes in the severity of specific PTSD symptoms or perhaps to other clinical variables (e.g., phasic shifts in symptom patterns, defensive organization, or different stages of decompensation or recompensation in response to treatment or to life events or changing conditions over time).

SOME PRELIMINARY LEADS RELATING T3 AND PSYCHOLOGICAL MEASURES

Core PTSD Symptoms

In a subgroup of 65 of the West Haven cohort patients, we were able to obtain ratings of PTSD symptoms together with hormonal measurements using the Clinician Administered PTSD Scale (CAPS-2), which provides three subscales measuring reexperiencing, avoidance, and hyperarousal symptoms on a state basis (21). The principal findings were that the CAPS total PTSD symptom score correlated significantly with total T3 ($r=.376$, $p<0.002$), with free T3 ($r=.309$, $p<0.01$) and total T4 ($r=.363$, $p<0.003$). Figure 8 presents a scatterplot of the total T3 and CAPS-2 total score data. With regard to the subscale data, the strongest correlations involving T3 were between the hyperarousal subscale score and levels of total T3 ($r=.407$, $p<0.0008$), and free T3 ($r=.352$, $p<0.004$). As might be expected, free T4 did not correlate significantly with any of the PTSD symptom measures. It is also interesting that total T3 was correlated significantly ($r=.291$, $p<0.02$) with the avoidance subscale score, while free T3 was significantly related ($r=.282$, $p<0.03$) to the reexperiencing subscale score (21). With regard to the 30 individual CAPS items, those showing the strongest correlations with TT3 and FT3 included feelings of being overwhelmed, increased startle, difficulty concentrating, hypervigilance, feeling as if a traumatic event were occurring, efforts to avoid activities or situations, and efforts to avoid thoughts or feelings. The main findings of significant relationships between the CAPS total and hyperarousal scores and both TT3 and FT3 were relatively strong, and were similarly found in both the first and sec-

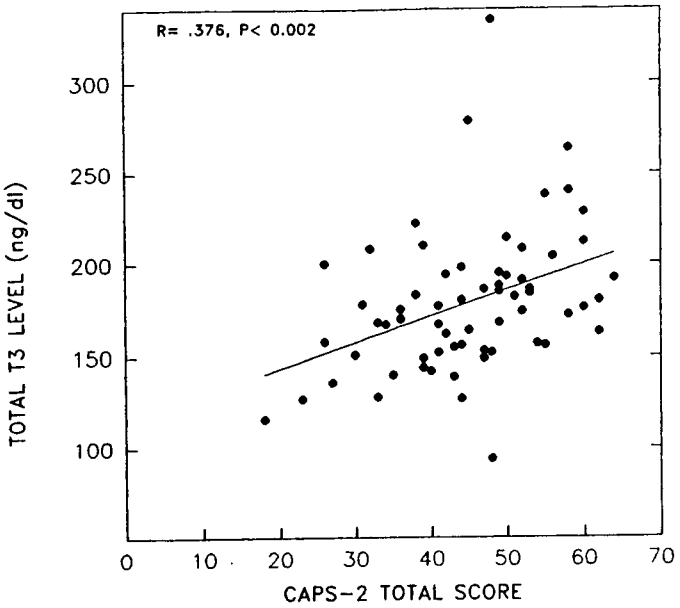

FIG. 8. Correlation between total T3 and CAPS-2 total score in PTSD.

ond halves of our West Haven sample of 65 patients.

It should be added, however, that the relationships between thyroidal and CAPS scores just cited did not reach significance in a smaller sample of PTSD patients (n=24) in the Menlo Park study. A search for possible explanations for the difference in findings between the two studies led to our awareness of some subtle but perhaps significant differences between the West Haven and Menlo Park programs in two areas, one involving clinical criteria for patient selection and the other involving clinical control of milieu conditions. Differences in the selection process of the Menlo Park program included exclusion of more severely ill patients meeting criteria for borderline personality disorder and those with prominent dissociative symptoms. With regard to ward milieu differences in the Menlo Park setting as an important element of treatment approach during the program, all patients were instructed *not* to discuss the war or traumatic memories with each other except in special treatment sessions for that purpose. As might be expected from these factors, the Menlo Park (MP) sample had significantly lower mean levels of CAPS scores than the West Haven (WH) sample, including the CAPS total score (WH=44.8±1.3 versus MP=32.9±2.5, t=4.60, p<0.00001), and the hyperarousal score (WH=17.0±0.4 versus MP=12.4±1.1, t=4.68, p<0.00001). As reported previously (8), there was also a tendency for lower T3 levels in the Menlo Park sample, so that lower mean levels and the associated compression of the range of both symptom and hormonal values in the Menlo Park sample may have accounted for the differences in correlational findings between the two studies.

This comparative study of two independent inpatient samples was one of the first of an increasing series of experiences to call our attention to the importance of detailed sample description—including careful definition of selection factors, severity of illness, clinical and study conditions affecting ward milieu, and other methodological details—in reporting and interpreting findings involving hormonal levels and their relationships with clinical or psychological measures in any given PTSD patient sample.

Other Clinical Features

From our early unpublished efforts to explore other possible relationships between thyroid hormones and prominent clinical features in our PTSD samples, it may be useful to cite two examples that provide further support for the need to attend carefully to the methodological concerns expressed in the previous section—involving details of sample description and study conditions in psychoendocrine studies of combat-related PTSD patients.

In an early subsample of 36 West Haven PTSD inpatients, some pilot work on dissociation by a member of our group (Bremner) led to the observation of a significant positive relationship between levels of total and free T3 and levels of dissociation, measured psychometrically. These relationships were, however, not significant in the Menlo Park sample of 24 patients, which showed a lower mean level and more narrow range of dissociation scores (a finding that may well be related to the policy of excluding patients with prominent dissociative symptoms in the Menlo Park program) and might logically be expected to reduce the likelihood of detecting significant relationships in the correlational analyses. Another possibly important methodological difference in the two studies was that the dissociation test was personally introduced and explained to the West Haven patients by a professional investigator with special interest in dissociation and expert knowledge of the psychometric instrument, whereas it was administered more impersonally as part of a larger package of assorted self-report psychometric tests in the Menlo Park study. In any event, this experience again appeared to dictate caution in approaching and interpreting "replication" psychoendocrine studies in PTSD without careful examination and comparison of patient sample and methodological factors that may be crucial to demonstrating relationships between particular clinical and hormonal features in this disorder.

A second example emerged from an interest of a member of our group (Southwick) in the possibility of novelty-seeking characteristics as a discriminating feature for a subtype of PTSD patient. This led to the observation in the Menlo Park sample (n=24) of significant positive correlations between both total and free T3 levels and a psychometric test score for novelty-seeking behavior, which appeared not simply to be related to severity of PTSD illness. These relationships, however, were not found when the same measurements were obtained in a subsequent subsample of West Haven patients, so that the question again was raised about whether or not differences between the patient samples or study conditions might possibly account for the difference in our correlational findings in the two studies. It may be, for example, that relationships between hormonal levels and clinical features such as novelty-seeking, which are generally thought of as trait or personality characteristics, are best demonstrated under relatively basal conditions, when state or stage of illness fluctuations (e.g., such as the elevated hyperarousal in the West Haven sample) are not superimposed in such a way as to obscure the more subtle long-term basal relationships. Another methodological difference in the two studies was that the psychometric and hormonal measures were obtained at the same point in time in the Menlo Park study, while there was considerable variability between the time of hormonal versus psychometric measurements in the West Haven sample; this perhaps raises the possibility of some state fluctuation in novelty-seeking behavior, even though it is generally viewed as an enduring characterological feature. Again, only further studies with careful attention to details of sample characterization, study conditions, and methodological factors will provide a more conclusive understanding of early leads such as these about possible relationships between clinical and hormonal aspects of PTSD.

GENERAL COMMENTS AND CONCLUSIONS

The finding of sustained elevations in levels of the metabolically potent hormone triiodothy-

ronine (T3) in many PTSD patients presents an interesting challenge in the investigation of the clinical significance of this unusual hormonal alteration, not only in terms of its possible linkage to PTSD symptoms, but also in relation to underlying psychological mechanisms that may have an important pathogenetic or clinical role in PTSD. Our initial efforts in this direction reviewed in the previous section must certainly be regarded as very preliminary, but they do provide encouragement and support for further work along these lines and present some leads suggesting potentially fruitful areas for further study. Our experience so far, however, has been perhaps most significant in drawing our attention repeatedly and forcefully to important issues concerning methodological rigor, quality control, and research strategy; these issues appear to be foundational for developing practical guidelines for the design and interpretation of future studies exploring the relationships between hormonal and clinical or psychological factors in PTSD patients.

Importance of Selection Factors in Patient Recruitment

There is a general tendency in research in biological psychiatry to define patient samples solely or largely by DSM-III-R diagnostic criteria and by ratings of severity of core symptoms of the primary illness. Our experience with combat-related PTSD patients within the VA hospital system, however, indicates that a number of additional clinical factors may require consideration in the screening process in order to characterize patient samples in sufficient detail to: 1) help **minimize heterogeneity** within a given patient sample, and 2) permit valid replication studies between different research centers. Some selection limitations are unavoidable, of course, such as our inability to include patients who seek isolation and avoid and refuse any hospital contact. Some patients may seek hospital treatment in a period of special crisis, but would not seek out or volunteer for any elective treatment program. Some will seek outpatient treatment help but decline participation in inpatient treatment programs. The inducements presented, restrictions imposed, or other factors associated with an inpatient treatment program that might influence the inclination of an individual patient to participate may further introduce selection bias in defining a particular patient sample. While patients in all the various categories just described may similarly meet DSM-III-R criteria for the diagnosis of PTSD and may even have comparable Mississippi scores, it appears inadvisable at this early stage of work in the field to assume that some may not represent biologically or clinically different subtypes of PTSD patients.

In recruiting patients for group-oriented longterm inpatient treatment programs, it is commonly a practical policy to exclude, for example, patients with a history of especially violent or asocial tendencies, or other behavior likely to cause ward or group management problems. Patients who are judged unlikely to be able to tolerate the demands and restrictions of a prolonged inpatient program also tend to be excluded. The issue of some VA patients viewing their acceptance into PTSD research or treatment programs as relevant to disability claims or economic advantage is widely recognized as another possible confounding element and one not always easy to assess in the screening process. Another variable that may naturally develop in research centers involved in longterm PTSD programs is the gradual modification of inclusion or exclusion criteria as the supply of new patients in a given region dwindles, in an effort to continue or expand the program. Our experience with psychoendocrine research at this preliminary stage suggests strongly that secondary selection factors such as those just mentioned should not be dismissed as minor, but should be included in the description of patient samples and considered in the interpretation of research findings until a sufficient database has been developed to establish the extent to which such variables may prove to be important to understanding relationships between hormonal and clinical factors in PTSD.

Importance of Clinical Subtyping and Comorbidity Assessment

Closely linked to selection factors described in the previous section is the issue of the desirability of defining and obtaining patient samples with as low a degree of heterogeneity as possible, for both clinical and research purposes. While many clinicians having extensive contact with PTSD patients have impressions about discriminating possible diagnostic subtypes, there appears to be no general agreement concerning the specific criteria that might best define or characterize such subtypes. There is a pressing need at this early stage in the field to generate and test hypotheses with both clinical and biological criteria that may identify clinically significant subtypes of PTSD patient samples. Such approaches could include not only the obvious criteria provided by comorbidity assessments, but also might be based upon clinical impressions involving specific psychological characteristics such as, for example, our pilot work on the novelty-seeking personality dimension as a possible basis for subtype discrimination. While this area is admittedly still in a preliminary exploratory stage, it is one that could have an extremely important strategic influence in facilitating future progress in this field and deserves considerable attention in our present efforts. From a tactical standpoint, however, it appears that any efforts to define patient subtypes must include careful evaluation of whether clinical or biological differences between patients represent enduring background or baseline differences versus episodic state, or phase differences at a particular point in their course of illness, as discussed in the next section.

Importance of Baseline Versus Phase Relationships

One very basic research strategy particularly highlighted by our preliminary work involves the need to consider both **phase** (acute, state, stage) and ongoing **basal** (chronic, trait, character) variables from a clinical and psychological standpoint. Hyperarousal, for example, may primarily represent the phase category, while novelty-seeking may be an example predominantly reflecting the basal category. It is very evident, however, that the two categories are not mutually exclusive, and that some variables showing appreciable acute or episodic fluctuations may also show enduring baseline alterations and, conversely, that some variables that appear predominantly to represent characterologic features may also show phase changes at times. Perhaps the generally intractable clinical course of PTSD favors the possibility that an understanding of the chronic baseline influences may yield the most insight into the pathogenesis of this disorder, and perhaps the most leverage in defining diagnostic subtypes. However, there is clearly a need to establish first the extent, magnitude, and relative importance of phase fluctuations in PTSD patients.

It appears, therefore, important to move in the direction of **longitudinal studies** with repeated hormonal and psychometric measurements over periods of many weeks or months in order to discriminate between phase and baseline relationships, as well as to learn more about the time relationships and the direction of the interactions between hormonal and psychological mechanisms. At this stage in the development of the field, it also appears very advisable to obtain the psychometric assessments, whether viewed as primarily phase or basal measures, as closely as possible to the time of the collection of hormonal samples, preferably on the same day or the following day.

Importance of Milieu Factors

Our experience in the VA hospital system with the study of PTSD inpatients in a treatment program organized within a group or cohort framework has impressed us with the importance of taking social factors carefully into account in the interpretation and reporting of psychoendocrine findings in PTSD patients. It is our impres-

sion, for example, that PTSD patients participating in intensive treatment and research programs, which involve living in a 12-patient cohort with constant group interaction over a 12-week period, tend to sustain higher urinary cortisol levels than PTSD patients studied on an individual basis in a mixed-diagnosis ward or on an outpatient basis. We have not as yet been able to look closely at this factor in relation to the thyroid system, but it appears very important to compare the thyroid profile in PTSD patients under highly protective, sanctuary-like conditions—in contrast to heavy-demand, group-oriented conditions—cross-sectionally but especially longitudinally, studying the same individual patient in such contrasting social and treatment settings.

Validity Questions Concerning Psychometric Assessments in PTSD

Another important issue in our experience relates to methodological questions concerning the administration and interpretation of psychometric tests in PTSD studies. In beginning a survey of the results obtained so far with a battery of about 20 psychometric methods in our PTSD patient cohorts, questions have repeatedly arisen concerning the accuracy of self-report test data or even clinician-administered test data depending largely on the verbal response of patients to questions. The problem may even begin with the conditions under which psychometric tests are administered. Variables such as the authority status, style, or attitude of the person presenting and explaining the tests, the attitude of the patients toward that person, the number of tests given consecutively and the time duration of the test session, and the nature of group interaction before and during the session might potentially influence test responses.

It is widely recognized that PTSD patients, particularly in the VA hospital setting, tend to exaggerate or over-endorse their symptomatology in response to direct self-report questionnaires. In looking at MMPI-2 validity measures in our patient sample, mean scores on the "F" validity scale and the Back-page Infrequency Scale, for example, are particularly high—around 100. The "F" scale was originally designed so that high scores would detect deviant or atypical ways of responding to test items, but such ways can range from indicating random responding to: 1) faking bad symptoms; 2) exaggerating symptoms as a plea for help or for self gain; 3) defiant resisting of the testing procedure; 4) short attention span; 5) withdrawal; 6) delusions or other psychiatric symptoms; or 7) perhaps responding simply from a deep need to maintain an acceptable self image. The Back-page Infrequency Scale high score is somewhat similar to the "F" scale score in that it may reflect such deviant responding as faking bad symptoms or over-endorsing items, but it also can indicate that the patient began to lose attention and concentration as the test progressed, and shifted to a largely random pattern of responding. There is a need for keen and clinically sensitive judgment in determining how to conceptualize and deal with these validity questions in evaluating not only MMPI data, but psychometric data in general that is obtained from PTSD patients. Clinical insight may even be useful in guiding the modification of certain standard psychometric instruments in accordance with idiosyncratic features in the perspective or style of many PTSD patients.

Until more guidelines are developed in this area, it may be a valuable strategy in the assessment of specific features in PTSD patients to use whenever possible an array of psychometric methods, including a self-report, and a clinician-administered, projective, and global clinical measurement of the feature in question. The use of projective tests and global clinical assessments, though generally considered less objective and quantitative than the more structured and operationally-defined procedures, may in fact deserve much wider consideration for trial in PTSD studies as instruments that may help in evaluation of the accuracy of self-report problems in this disorder. Other more standard tactics, such as eliminating patients from the data analysis who are extreme outliers on the validity measures of the MMPI or stratifying patients on the basis of validity or personality measures, may also be useful in teasing out the true rela-

tionships between psychological and hormonal factors.

Finally, while our preliminary findings suggest that such particular psychological or clinical features as hyperarousal, dissociation, or novelty-seeking behavior may have special relationships to the T3 elevations in PTSD, these observations clearly only represent a beginning in a broader survey that remains to be done, especially perhaps with further assessments in two areas. The first area involves a need to find or develop instruments that will provide valid and reliable measurement of PTSD symptoms that are closely similar to those reported in clinical hyperthyroidism, including sleep disturbances, startle, irritability, explosive anger, difficulty in concentrating, and restlessness. Such measures would permit the study of the possible role of T3 elevations in relation to these important symptoms and impairing factors in PTSD, and perhaps contribute to ideas concerning possible treatment studies linked to thyroid alterations in PTSD. The second area involves the need for assessment of personality or character disorder factors, perhaps including coping and defensive styles, which may be especially likely to be linked with hormonal measures (20) and are a prominent part of the clinical picture in PTSD patients.

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